RENAL FUNCTION IN WILSON'S DISEASE[1]

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Wilson's disease (hepatolenticular degeneration) is an hereditary disorder characterized by a variety of metabolic defects. There is excessive absorption of copper from the intestinal tract (1, 2) and, as a consequence, an increase in the total copper content of the body, particularly in the brain, liver (3) and kidneys (4). The serum ceruloplasmin, the main copper-carrying protein present in the serum, is abnormally low (5, 6). The total serum copper concentration also is lower than normal (6, 7), although the small fraction of copper bound to serum albumin, designated by Cartwright and his co-workers as the "direct-reacting copper," is increased (7). There is excessive urinary excretion of copper (8).

The finding of marked aminoaciduria in patients with Wilson's disease by Uzman and Denny-Brown in 1948 (9) revealed still another metabolic abnormality which occurs in many but not all cases (10). There may also be increased urinary urate excretion, accompanied by a moderate decrease in the serum urate level (11). Glycosuria, in the absence of a raised blood glucose concentration, is an occasional additional finding (12).

The occurrence of marked aminoaciduria, uricosuria and glycosuria in some patients with Wilson's disease suggests the possibility of renal involvement in this disorder (12). Little information is available concerning the nature and extent of the presumed renal defect (13, 14).

The present investigation was designed to afford a more composite analysis of discrete renal functions in Wilson's disease by applying simultaneous clearance techniques. A preliminary report of some of the results has appeared elsewhere (15).

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CASES AND METHODS

The nine patients studied were in varying stages of the disease (Table I). The manifestations of the disorder in these patients were predominantly neurological. None gave evidence of advanced cirrhosis of the liver and none had ascites. All of the patients had a decreased serum ceruloplasmin. In eight of the nine patients the total serum copper excretion was reduced. The urinary copper excretion was excessive in every instance. The daily urinary output of α-amino nitrogen was increased, or an increase could readily be induced by a high protein intake. All of the patients had received considerable quantities of BAL medication but this was discontinued for at least three days prior to the clearance study.

Eleven renal clearance studies were performed in these nine patients, using standard techniques (16). The glomerular filtration rate was measured by inulin clearance; renal plasma flow by clearance of para-aminohippurate; tubular excretory mechanisms in six instances by estimation of Tm_{PAH}; tubular reabsorptive mechanisms by clearances of amino acids, urate and phosphate, and in four patients also by estimation of Tm glucose. As a further measure of tubular excretory and reabsorptive capacities, the inhibiting effect of probenecid on tubular transport of PAH and urate was studied in seven patients. The excretion of bicarbonate and titratable acid was determined in four patients.

All experiments were performed in the morning with the patient in the fasting, post-absorptive state. To ensure adequate urine flow for the duration of the clearance experiments, liberal quantities of water were administered orally. Three or four urine collections were made by indwelling catheter in every experiment, each collection comprising a period of 20 minutes; in the experiments with probenecid, six 20-minute collections were made. When the determination of bicarbonate was to be included in the analysis, the customary air insufflation and bladder wash were omitted, and paraffin oil was used to prevent loss of CO_2. Urine pH determinations were made by means of a Cambridge pH meter as soon as each urine sample was procured.

Two patients (Cases Y.R. and L.A.) were hospitalized and maintained on a constant diet of 2,500 calories. After a control period of six days, ammonium chloride in syrup of cherry was administered for four successive days in doses of 10, 14, 14 and 16 Gm. per day, respectively. Observations were continued for five days after cessation of medication. The urine, preserved with tolu-

TABLE I

General description of the nine cases of Wilson's Disease studied

Name Sex Age	Approximate duration of overt disease	Clinical severity*	Osteomalacia or bone fragmentation	Albuminuria†
	years			*mg./24 hours*
M. F. Male 40	3	+++	0	<10
R. V. Male 13	4	+	0	<10
M. G. Male 33	5	+	+	180
C. P. Male 27	6	+	0	270
P. C. Female 36	7	++	+	<10
F. L. Male 35	8	+	+	20
L. A. Male 53	20	+	0	140
Y. R.‡ Female 37	23	++	+	
B. R.‡ Female 37	23	++	0	60

* Clinical severity: + Mildly incapacitated but employable, ++ Severely incapacitated, +++ Bedridden.
† Normal range (10 to 20 mg. per 24 hours).
‡ Uniovular twins.

ene, was collected daily throughout the 15-day period of study and the pH, titratable acid, and bicarbonate were determined.

Analytical methods. Inulin, para-aminohippurate, urate, phosphate, ammonia, titratable acid, and creatinine were determined by the standard procedures indicated elsewhere (17). In estimating glucose Tm, samples for inulin analysis were digested with baker's yeast before color development with diphenylamine, instead of the Roe method employed otherwise for determination of inulin. Glucose was determined by the Folin and Wu method. Plasma α-amino acid nitrogen was estimated by the method of Hamilton and Van Slyke (18), urinary α-amino acid nitrogen by the method of Van Slyke, MacFadyen, and Hamilton (19). Plasma and urinary bicarbonate were determined by Van Slyke's manometric technique. The urinary excretion of albumin was estimated by an immunological technique (20).

RESULTS

Except in one instance (Case R.V.), the *glomerular filtration rate,* as measured by the inulin clearance, was reduced (Table II). The reduction was moderate in Cases M.F., P.C., C.P., M.G., and F.L. (range, 76.2 to 91.9 ml. per min.), more pronounced in Cases L.A., Y.R., and B.R. (range, 48.9 to 69.0 ml. per min.).

As another indication of glomerular involvement, the urinary excretion of albumin was increased in Cases C.P., M.G., L.A., and B.R. (270, 180, 140, and 60 mg. per 24 hours, respectively). In the remaining four cases, the urinary excretion of albumin was within the normal range (< 10 to 20 mg. per 24 hours) by the immunologic method employed. The blood urea nitrogen was not elevated in any of the patients.

Renal plasma flow, as measured by clearance of para-aminohippurate, was consistently reduced. In six cases, C_{PAH} ranged from 453 to 342 ml. per min. In two patients (Cases L.A. and Y.R.), C_{PAH} was less than 250 ml. per min. (Table II). The filtration fraction, C_{inulin}/C_{PAH}, was somewhat higher than normal in most instances, with a mean of 0.238. The blood pressure was normal in every instance.

Tubular excretory capacity, as measured by Tm_{PAH}, was invariably reduced in the six patients examined (Table II). In four instances (Cases M.F., M.G., L.A., and Y.R.), the values obtained were below 40 mg. per min.; in Cases P.C. and F.L., Tm_{PAH} was 59.1 and 43.5 mg. per min., respectively.

Tubular reabsorptive mechanisms, in respect to α-amino nitrogen, urate, inorganic phosphate and glucose, were found to be impaired (Table II).

The $C_{\alpha\text{-}NH_2N}/C_{inulin}$ ratio in six of the nine cases was considerably increased. The highest values were found in the three cases of longest duration of overt disease (L.A., Y.R., and B.R.), in whom $C_{\alpha\text{-}NH_2N}/C_{inulin}$ was 15.8 per cent, 10.0 per cent and 16.8 per cent, respectively. (Normal range, 1.0 per cent to 3.0 per cent). The plasma α-amino nitrogen in these patients did not differ significantly from normal.

The plasma *urate* was less than 3.0 mg. per cent in six patients (2.0 mg. per cent in Case B.R.), and in the remainder varied between 3.0 and 3.9 mg. per cent—all below the minimum normal level

by the analytical method employed. (Normal range, 4.0 to 6.0 mg. per cent). C_{urate} was uniformly increased, in four instances exceeding 20 ml. per min. This increase is even more striking when the reduced glomerular filtration rate is taken into account; the mean C_{urate}/C_{inulin} was 28.0 per cent, range from 15.4 to 46.7 per cent.

The plasma *inorganic phosphate* was in the lower range of normal in five of the six cases examined (2.4 to 3.3 mg. per cent) and distinctly reduced in one instance (Case L.A., 1.5 mg. per cent). Phosphate clearance exceeded the normal in each of these six cases, ranging from 18.7 to 37.1 ml. per min., with a mean of 25.8 ml. per min. Calculation of the ratio, C_{PO_4}/C_{inulin}, emphasized the increase in phosphate clearance, the mean value obtained being 34.1 per cent.

The fasting blood *glucose* in the four patients in whom it was measured (Cases M.G., M.F., F.L., and C.P.) was at low normal levels (78, 84, 87 and 87 mg. per cent, respectively). The glucose Tm was measured in these four patients. In two, the results obtained were somewhat below the lower limit of the normal range (Cases M.F. and F.L., 272 and 246 mg. per min., respectively). In one instance (Case M.G.), the glucose Tm was reduced to 184 mg. per min. In Case C.P. the value obtained was strikingly low, 95 mg. per min. None of these patients had spontaneous glycosuria or hypoglycemia. Occasional spontaneous glycosuria was present in three cases (L.A., B.R., Y.R.).

Effect of probenecid on tubular transport mechanisms (Table III)

Probenecid is a potent inhibitor of renal tubular excretory systems (21), markedly suppressing tubular transport of PAH (17, 22); this effect is less pronounced if the transport mechanisms are deficient, the diminished effect thus serving as a further indication of the degree of impairment of tubular excretory mechanisms. In two patients with clinical manifestations of Wilson's disease of relatively short duration (approximately five years), probenecid given intravenously in a dosage of 26 to 32 mg. per Kg. body weight reduced Tm_{PAH} significantly, from 59.1 to a minimum of 22.6 (Case P.C.); and from 39.2 to a minimum of 29.5 mg. per min. (Case M.G.). This response

TABLE II

Renal clearance studies in nine patients with Wilson's Disease *

Name	C_{In}	C_{PAH}	Tm_{PAH}	$P_{\alpha\text{-}NH_2N}$	$C_{\alpha\text{-}NH_2N}$	P_{Urate}	C_{Urate}	P_{PO_4}	C_{PO_4}	TmG	$\frac{C_{In}}{C_{PAH}}$	$\frac{C_{\alpha\text{-}NH_2N}}{C_{In}}$	$\frac{C_{Urate}}{C_{In}}$	$\frac{C_{PO_4}}{C_{In}}$	Urine pH
	(ml./min.)	(ml./min.)	(mg./min.)	(mg. %)	(ml./min.)	(mg. %)	(ml./min.)	(mg. %)	(ml./min.)	(mg./min.)	(%)	(%)	(%)	(%)	
M. F.	91.9	422		3.5	2.9	3.5	15.3	2.4	28.0		21.9	3.1	16.7	30.4	6.6–6.8
	90.5		37.9			3.9	14.0			272			15.5		6.8–7.2
R. V.	107.0	453		4.8	4.9	2.4	32.4	3.3	37.1		23.6	4.6	30.2	34.7	7.1–7.3
M. G.	89.7	360	39.2	4.6	6.3	2.4	25.6	2.5	22.4		24.9	7.0	28.4	25.0	6.8–7.3
	79.0	342								184	23.1				
C. P.	85.7	345		4.4	2.5	3.7	13.2			95	24.8	2.9	15.4		6.6–7.2
P. C.	76.2	371	59.1	4.3	4.4	2.6	17.5	2.5	18.7		20.6	5.8	23.0	24.5	
F. L.	83.2	360	43.5	3.9	1.1	2.8	24.0			246	23.1	1.3	28.9		6.9–7.0
L. A.	48.9	199	14.5	4.4	7.7	3.0	18.7	1.5	28.8		24.6	15.8	38.2	59.0	7.7–8.0
Y. R.	63.5	233	21.5	4.9	6.4	2.5	16.2	2.5	19.5		27.3	10.0	25.5	30.7	
B. R.	69.0			3.6	11.6	2.0	32.2					16.8	46.7		7.2–7.5
Normal values	♂ 124±25.8	654±163	79.8±16.7	3.4–5.5	1.0–3.0	4.0–6.0	8.0±2.0	3.0–5.0	10.0–12.0	350±50	19.2±3.5	1.0–3.0	7.0±2.0	10.0	
	♀ 108±13.5	592±153													

* The patients are listed in order of increasing duration of overt disease.
All clearance values are corrected to standard body surface area (1.73 $M.^2$). All values are means of three or four 20-minute clearance periods.
All normal values except for α-amino acid nitrogen and urate are quoted from References 29 and 33.

TABLE III

Effect of probenecid on C_{In}, C_{PAH} (or Tm_{PAH}) and C_{Urate} in seven patients with Wilson's Disease

Name	Dosage of probenecid	C_{In}		C_{PAH}			Tm_{PAH}			C_{Urate}		
		Control*	After probenecid†	Control	After probenecid		Control	After probenecid		Control	After probenecid	
					Mean	Minimum		Mean	Minimum		Mean	Peak
	(*mg./Kg.*)											
M.F.	40, I.V.	91.9	91.8	422	243	193				15.3	35.7	38.0
R.V.	40, I.V.	107.0	129.0	453	279	212				32.4	51.6	58.9
F.L.	40, I.V.	65.3	65.8	341	201	175				14.3	34.7	38.4
M.G.	32, P.O.	89.7	84.4	360			39.2	32.9	29.5	25.6	25.7	34.3
P.C.	27, P.O.	76.2	71.7	371			59.1	32.9	22.6	17.5	26.7	32.4
L.A.	28, P.O.	48.9	52.2	199			14.5	11.5	8.6	18.7	22.1	24.1
Y.R.	26, P.O.	63.5	63.0	233			21.5	22.4	20.0	16.2	21.8	23.4
Means		77.5	79.7	405 (3 cases)	241	193	33.6	24.9	20.2	20.0	31.2	35.6

* All control values represent the means of three or four 20-minute periods. All control and post-medication values are corrected to standard body surface area of 1.73 M.²

† All values after probenecid represent the means of six or seven 20-minute periods.

was somewhat less marked, however, than that of a normal subject in whom probenecid in oral dosage of 20 mg. per Kg. body weight reduced Tm_{PAH} from 83.4 to 26.4 mg. per min. (17). In two patients with symptoms of some 20 years' duration (Cases L.A. and Y.R.: Tm_{PAH} 14.5 and 21.5 mg. per min., respectively), probenecid elicited, at most, an equivocal further depression of Tm_{PAH}. In three patients (Cases M.F., R.V., and F.L.), whose clinical symptoms were of relatively short duration, and whose initial C_{PAH} was but moderately reduced (422, 453, 341 ml. per min.), there was marked further suppression of C_{PAH} by probenecid. The response did not seem to differ in degree from that of (gouty) subjects with intact kidney function (17).

Probenecid markedly suppresses tubular reabsorption of urate and thus increases urate clearance in the intact kidney. In 10 gouty subjects with little or no renal damage, probenecid in oral dosage of 20 to 30 mg. per Kg. body weight evoked an increase in C_{urate} of approximately 300 per cent, from a mean of 8.5 ml. per min. to peak values averaging 32.9 ml. per min. (range, 10.2 to 51.3 ml. per min.) (17). In the seven patients with Wilson's disease examined, there was an increase in C_{urate} of approximately 75 per cent after intravenous administration of probenecid in comparable dosage, from a mean of 20 ml. per min. to a mean peak of 35.6 ml. per min. This poor percentile response is attributable in part to the high initial C_{urate}. The results in the two patients with symptoms of longest duration (Cases L.A. and Y.R.), in whom C_{urate} increased from 18.7 to a peak of only 24.1 ml. per min. and from 16.2 to 23.4 ml. per min., respectively, suggest deficient tubular response to probenecid. The findings in these two patients were comparable to those obtained in the Fanconi syndrome, in which there was no response to probenecid (17, 23).

Effect of ammonium chloride acidosis

It was observed in the course of the foregoing renal clearance studies that the urine pH ranged from 6.6 to 8.0 (Tables II and IV). This prompted measurement of urinary bicarbonate excretion which, in the four patients studied (Cases M.F., M.G., C.P., and F.L.), was found to vary from 0.088 to 0.034 mM per min. at levels of plasma bicarbonate ranging from 25.0 to 20.7 mM

TABLE IV

Bicarbonate excretion in four patients with Wilson's Disease

Name	Urine flow	C_{IN}	Plasma $BHCO_3$	Urine pH	Urine $BHCO_3$	Urine H^+	$BHCO_3$ filtered	$BHCO_3$ reabsorbed	$BHCO_3$ filtered	$BHCO_3$ reabsorbed
	(*ml./min.*)	(*ml./min.*)	(*mM/L.*)		(*mM/min.*)	(*mM/min.*)	(*mM/min.*)	(*mM/min.*)	(*mM/100 ml. glomerular filtrate*)	
M. F.	9.8–16.1	90.5	25.0	6.8–7.1	0.088	0.002	2.26	2.17	2.50	2.40
F. L.	3.2–14.1	83.2	20.7	6.9–7.0	0.046	0.013	1.72	1.67	2.07	2.01
C. P.	5.8– 9.4	85.7	22.0	7.0	0.062	0.010	1.89	1.83	2.20	2.14
M. G.	4.0– 9.3	79.0	22.0	6.8	0.034	0.010	1.74	1.71	2.20	2.16

per L. The results (Table IV) suggest that tubular reabsorption of bicarbonate may not be quite as efficient in some patients with Wilson's disease as in the normal subject.

Ammonium chloride acidosis was produced in Patients Y.R. and L.A. In the six-day control period, Case Y.R., in whom overt Wilson's disease was of longest duration, excreted 18.8 to 26.4 mM bicarbonate per day (mean, 21.7 mM per day) at a mean plasma bicarbonate level of 23.1 mM per L. The urine pH varied from 6.9 to 7.2, the titratable acid averaged 4.4 mEq. per day. With induction of acidosis (plasma bicarbonate reduced to a minimum of 14.6 mM per L.), the urine pH fell to a low of 4.9, the titratable acid increased to a maximum of 38.0 mEq. per day, bicarbonate disappeared from the urine.

A similar response was noted in Case L.A. In the six-day control period, the excretion of bicarbonate varied from 11.1 to 16.5 mM per day (mean, 14.1 mM per day) at a mean plasma bicarbonate level of 27.6 mM per L. The range of urine pH was 6.2 to 7.0, the titratable acid averaged 11.7 mEq. per day. Administration of ammonium chloride reduced the plasma bicarbonate level to a minimum of 19.1 mM per L. and the urine pH to a low of 5.1. The titratable acid increased to a maximum of 41.9 mEq. per day, urinary bicarbonate excretion became negligible.

The urinary excretion of ammonia in Cases Y.R. and L.A. was within normal limits (means, 25.2 and 22.7 mEq. per day, respectively) in the control period.

DISCUSSION

The results of these renal clearance studies confirm and amplify previous reports indicating impairment of tubular transport systems and renal hemodynamics in patients with Wilson's disease, at least in its more advanced stages. Some hitherto unrecorded abnormalities are described.

Hodges and co-workers (13, 14) noted marked and consistent reduction in C_{PAH} and equivocal decline in C_{inulin} in their study of four cases of Wilson's disease. The present investigation corroborates the substantial reduction in renal plasma flow and discloses distinctly decreased glomerular filtration rate in most instances. The degree of impairment seemed roughly to parallel the severity or duration of overt disease in this series of patients, suggesting progressive deterioration of the renal vascular bed.

The tubular secretory capacity, as measured by Tm_{PAH}, was found to be reduced, strikingly so in the more advanced cases. Associated with this decline was a diminishing effect of probenecid in eliciting a further reduction in Tm_{PAH}.

Impairment of renal tubular reabsorptive activities in Wilson's disease has been suspected for some time. The excessive aminoaciduria, for example, has been attributed to inadequate tubular reabsorption (12, 24). This interpretation is supported by the high values obtained for $C_{\alpha\text{-}NH_2\text{-}N}$, and particularly for $C_{\alpha\text{-}NH_2\text{-}N}/C_{inulin}$, in the face of normal plama levels of α-amino nitrogen. Similarly, diminished tubular reabsorption of filtered urate, suggested by Bishop, Zimdahl, and Talbott (11) and Mahoney, Sandberg, Gubler, Cartwright, and Wintrobe (25), to explain the uricosuria and low plasma urate levels noted by them in patients with Wilson's disease, is indicated by the augmented urate clearance ratios consistently observed in the present study. The capacity of probenecid further to increase C_{urate}/C_{inulin} decreased as the tubular transport systems for urate deteriorated with progress of the disease, until the drug finally was quite ineffective, as in the Fanconi syndrome.

In all six of the patients so studied, an increase in C_{PO_4} was observed, and in five of these the serum inorganic phosphate was in the low normal range or reduced. Cooper, Eckhardt, Faloon, and Davidson (12) described a patient with Wilson's disease who was reputed to have had hypophosphatemia prior to their study. Warnock (26) reported a patient with Wilson's disease with spontaneous fractures, demineralization of bone, and a plasma inorganic phosphate level of 2.5 mg. per cent. The low serum phosphate and increased renal clearance of phosphate may be responsible, in part, for the occasional occurrence of osteomalacia in this disease (12, 26, 27).

The observation that glycosuria may be present in some patients with Wilson's disease has been somewhat amplified in the present study, in which the tubular reabsorptive capacity for glucose was measured. It is noteworthy that, although spontaneous glycosuria was not usually present, the maximum tubular capacity to reabsorb glucose was reduced in varying degree in all four cases studied. These findings emphasize the fact that failure to find increased urinary excretion of glucose in Wilson's disease does not preclude a very considerable defect in the capacity of the renal tubules to transport glucose across the tubular epithelium.

The tendency to excrete urine of high pH, due to renal excretion of small quantities of bicarbonate at plasma bicarbonate levels which should not be associated with urinary loss (28), suggests that there may be slight impairment of tubular reabsorption of bicarbonate in advanced stages of Wilson's disease. When ammonium chloride acidosis was induced, there was a prompt decline in urine pH, increase in titratable acidity, and disappearance of urinary bicarbonate.

The precise mechanisms involved in the impairment of tubular functions observed in Wilson's disease must remain speculative so long as the normal mechanisms of renal tubular transport are poorly understood (29). The hypothesis that the renal lesion is a primary effect of the abnormal gene on the functional integrity of the renal tubule receives little support from this study. That the abnormal gene may result in an anatomical defect of the renal tubule, not necessarily related to the described functional abnormalities, is suggested by the preliminary observations of Soothill and Kark (30). They have observed a deformity in the proximal convolution of the tubule in renal biopsy specimens obtained from patients with Wilson's disease. It was not apparent to them whether this abnormality was primary, as in the Fanconi syndrome, or whether this was due to a local change resulting from Wilson's disease. Darmady (31), however, was unable to discern any anatomical defect in the proximal renal tubules in the kidneys of patients who had died of Wilson's disease. But although the details of the pathogenesis of the disease and its varied manifestations remain largely unknown, a plausible hypothesis to explain the renal lesions can be tentatively suggested as a result of this study. The deficiency of serum ceruloplasmin in Wilson's disease is associated with an increase in the copper loosely bound to serum albumin. This loosely bound copper can be deposited in any tissue where there are substances which can compete successfully with albumin for the copper ion. With increased deposition of copper in the kidney, the metal may interfere with essential enzyme systems responsible for the transport of materials across the tubular epithelium, such as is presumed to occur in chronic poisoning with other divalent metals (32). Initially, the brunt of the damage falls predominantly on the proximal renal tubule, resulting in defective transport of PAH, phosphate, urate, amino acids, and glucose, in these respects resembling somewhat the defects occurring in Fanconi syndrome. This emphasizes the desirability of excluding Wilson's disease in patients with defective renal tubular functions.

With progression of the renal lesion, other functions of the kidney are disturbed and the functional abnormality is no longer restricted to any anatomical segment of the renal tubule. A decreased glomerular filtration rate, and a tendency to excrete an alkaline urine, indicate more widespread renal damage.

SUMMARY

1. Eleven renal clearance studies were carried out in nine patients with Wilson's disease in various stages of the disorder.

2. The inulin clearance was below the lower limits of normal in eight patients. C_{PAH} was decreased in every instance.

3. Tubular secretory capacity, as measured by Tm_{PAH}, was reduced in the six patients examined. When Tm_{PAH} was very low, probenecid elicited little further decrease.

4. Tubular reabsorption of α-amino nitrogen, urate, phosphate, and glucose was defective, as indicated by the generally increased clearance ratios. Serum inorganic phosphate levels were in the lower range of normal or reduced, and may account for the osteomalacia occasionally encountered in Wilson's disease. The blood glucose was in the low normal range. The Tm glucose tended to be low in the four patients so studied, probably explaining the occasional glycosuria in this disorder. Serum urate levels were consistently low. Probenecid elicited a uricosuric response in most instances but this was least pronounced in those subjects who initially had the most impaired tubular reabsorption of urate.

5. The urine pH tended to be more alkaline than normal, owing to slight urinary excretion of bicarbonate at plasma bicarbonate levels not ordinarily associated with renal loss of bicarbonate. The response of two subjects to ammonium chloride-induced acidosis was essentially normal in respect to mechanisms for acidification of the urine.

6. The results indicate progressive deterioration of certain discrete tubular functions, and also of glomerular filtration and renal plasma flow, with advance of the disease. It is suggested that these renal changes may reasonably be ascribed to the deleterious effects of the accumulation of copper in the kidneys; such effects are known to accompany the deposition of other heavy metals in this organ. In this view the renal abnormalities described are secondary to a disturbance in copper metabolism rather than a direct consequence of the abnormal gene on renal function.

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